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(54) Title: SULFONAMIDES

(57) Abstract: The present invention relates to sulfonamides, pharmaceutical compositions containing them, and their use as antagonists of urotensin II.

SULFONAMIDES

FIELD OF THE INVENTION

The present invention relates to sulfonamides, pharmaceutical compositions containing them and their use as urotensin II antagonists

BACKGROUND OF THE INVENTION

The integrated control of cardiovascular homeostasis is achieved through a combination of both direct neuronal control and systemic neurohormonal activation. Although the resultant release of both contractile and relaxant factors is normally under stringent regulation, an aberration in this *status quo* can result in cardiohemodynamic dysfunction with pathological consequences.

The principal mammalian vasoactive factors that comprise this neurohumoral axis, namely angiotensin-II, endothelin-1, norepinephrine, all function via an interaction with specific G-protein coupled receptors (GPCR). Urotensin-II, represents a novel member of this neurohumoral axis.

In the fish, this peptide has significant hemodynamic and endocrine actions in diverse end-organ systems and tissues:

- smooth muscle contraction

  both vascular and non-vascular in origin including smooth muscle preparations from the gastrointestinal tract and genitourinary tract. Both pressor and depressor activity has been described upon systemic administration of exogenous peptide

- osmoregulation:

  effects which include the modulation of transepithelial ion (Na^+, Cl^-) transport. Although a diuretic effect has been described, such an effect is postulated to be secondary to direct renovascular effects (elevated GFR)

- metabolism:

  urotensin-II influences prolactin secretion and exhibits a lipolytic effect in fish (activating triacylglycerol lipase resulting in the mobilization of non-esterified free fatty acids)

  (Pearson, *et. al. Proc. Natl. Acad. Sci. (U.S.A.)* **1980**, *77*, 5021; Conlon, *et. al. J. Exp. Zool.* **1996**, *275*, 226.)

In studies with human Urotensin-II it was found that it:

- was an extremely potent and efficacious vasoconstrictor
- exhibited sustained contractile activity that was extremely resistant to wash out
- had detrimental effects on cardiac performance (myocardial contractility)

Human Urotensin-II was assessed for contractile activity in the rat-isolated aorta and was shown to be the most potent contractile agonist identified to date. Based on the *in vitro* pharmacology and *in vivo* hemodynamic profile of human Urotensin-II it plays a pathological role in cardiovascular diseases characterized by excessive or abnormal vasoconstriction and myocardial dysfunction. (Ames *et. al. Nature* **1999**, *401*, 282; Douglas & Ohlstein (2000). Trends Cardiovasc. Med., 10(6):229-37)

Compounds that antagonize the Urotensin-II receptor may be useful in the treatment of congestive heart failure, stroke, ischemic heart disease (angina, myocardial ischemia), cardiac arrhythmia, hypertension (essential and pulmonary), COPD, fibrosis (e.g. pulmonary fibrosis), restenosis, atherosclerosis, dyslipidemia, asthma, (Hay DWP, Luttmann MA, Douglas SA: 2000, Br J Pharmacol: **131; 10-12**) neurogenic inflammation and metabolic vasculopathies all of which are characterized by abnormal vasoconstriction and/or myocardial dysfunction. Urotensin antagonists may provide end organ protection in hypersensitive cohorts in addition to lowering blood pressure.

Since U-II and GPR14 are both expressed within the mammalian CNS (Ames *et. al. Nature* **1999**, *401*, 282), they also may be useful in the treatment of addiction, schizophrenia, cognitive disorders/Alzheimers disease, (Gartlon J. Psychopharmacology (Berl) 2001 June; 155(4):426-33), impulsivity, anxiety, stress, depression, pain, migraine, neuromuscular function, parkinsons, movement disorders, sleep-wake cycle, and incentive motivation (Clark *et al.Brain Research* 923 (2001) 120-127.

Functional U-II receptors are expressed in rhabdomyosarcomas cell lines and therefore may have oncological indications. Urotensin may also be implicated in various metabolic diseases such as diabetes (Ames *et. al. Nature* **1999**, *401*, 282, Nothacker et al., *Nature Cell Biology* 1: 383-385, 1999) and in various gastrointestinal disorders, bone, cartilage, and joint disorders (e.g. arthritis and osteoporosis); and genito-urinary disorders. Therefore, these compounds may be useful for the prevention (treatment) of gastric reflux, gastric motility and ulcers, arthritis, osteoporosis and urinary incontinence.

SUMMARY OF THE INVENTION

In one aspect this invention provides for sulfonamides and pharmaceutical compositions containing them.

In a second aspect, this invention provides for the use of sulfonamides as antagonists of urotensin II, and as inhibitors of urotensin II.

In another aspect, this invention provides for the use of sulfonamides for treating conditions associated with urotensin II imbalance.

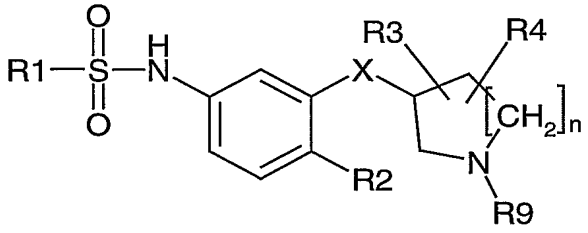
In yet another aspect, this invention provides for the use of sulfonamides for the treatment of congestive heart failure, stroke, ischemic heart disease (angina, myocardial ischemia), cardiac arrhythmia, hypertension (essential and pulmonary), renal disease (acute and chronic renal failure/end stage renal disease) along with peripheral vascular disease (male erectile dysfunction, diabetic retinopathy, intermittent claudication/ischemic limb disease) and ischemic/hemorrhagic stroke, COPD, restenosis, asthma, neurogenic inflammation, migraine, metabolic vasculopathies, bone/cartilage/joint diseases, arthritis and other inflammatory diseases, fibrosis (e.g. pulmonary fibrosis), sepsis, atherosclerosis, dyslipidemia, addiction, schizophrenia, cognitive disorders/Alzheimers disease, impulsivity, anxiety, stress, depression, parkinsons, movement disorders, sleep-wake cycle, incentive motivation, pain, neuromuscular function, diabetes, gastric reflux, gastric motility disorders, ulcers and genitourinary diseases.

The urotensin antagonist may be administered alone or in conjunction with one or more other therapeutic agents, said agents being selected from the group consisting of endothelin receptor antagonists, angiotensin converting enzyme (ACE) inhibitors, A-II receptor antagonists, vasopeptidase inhibitors, diuretics, digoxin, and dual non-selective β-adrenoceptor and α_1-adrenoceptor antagonists.

Other aspects and advantages of the present invention are described further in the following detailed description of the preferred embodiments thereof.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides for compounds of Formula (I):



Formula (I)

wherein:

R_1 is naphthyl, quinolinyl, benzothiophenyl, benzthiadiazoyl, benzoxadiazoyl, naphthoxadiazoyl, benzofuranyl, dibenzofuranyl, benzothiazoyl, benzoxazoyl, benzisoxazoyl, tetrahydrobenzopyranyl, chromenonyl, tetrahydrothienopyridinyl, benzimidazoyl,

benzodioxanyl, benzodioxoyl, benzodioxepinyl, naphthyridinyl, indoyl or quinazolinyl, indanyl, tetrahydronaphthyl, tetrahydroisoquinolinyl, imidazothioazolyl substituted or unsubstituted by one, two , three, four or five of any of the following: halogen, CF_3, OCF_3, SCF_3, NO_2, CN, C_{1-6} alkyl, C_{1-6} alkoxy, NR_5R_6, $CONR_7R_8$, SC_{1-6} alkyl, $CO_2(C_{1-6}$ alkyl), C_{1-6} alkyl-$CO_2(C_{1-6}$ alkyl), $COCF_3$, COR_{11};

R_2 is hydrogen, halogen, CF_3, CN, or C_{1-4} alkyl;

R_3, R_4, are independently hydrogen, C_{1-6} alkyl, benzyl, $-C(R_{13})_2$-OR_{11}, $-COOR_{12}$, $-CONR_{11}$, $-C(R_{13})_2$- $N(R_{11})_2$;

R_7, and R_8 are independently hydrogen, C_{1-6} alkyl, or benzyl;

R_5 and R_6, are independently hydrogen or C_{1-6} alkyl;

R_9 is hydrogen, C_{1-6} alkyl, or $-(CH_2)_mR_{14}$;

R_{11} is hydrogen or C $_{1-6}$ alkyl;

R_{12} is C $_{1-6}$ alkyl;

R_{13} is independently hydrogen or C_{1-3}alkyl;

R_{14} is phenyl, OH, or-$(C=O)C_{1-3}$alkyl;

X is O, S, or CH_2;

n is 0, 1 or 2;

m is 1 or 2;

provided that when R_{14} is OH, m is 2;

or a pharmaceutically acceptable salt thereof.

When used herein, the term "alkyl" includes all straight chain and branched isomers. Representative examples thereof include methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *sec*-butyl, *iso*-butyl, *t*-butyl, *n*-pentyl and *n*-hexyl.

When used herein, the terms 'halogen' and 'halo' include fluorine, chlorine, bromine and iodine, and fluoro, chloro, bromo and iodo, respectively.

The compounds of the present invention may contain one or more asymmetric carbon atoms and may exist in racemic and optically active form. All of these compounds and their diastereoisomers are contemplated to be within the scope of the present invention.

R_1 is preferably naphthyl, quinolinyl, benzothiophenyl, benzthiadiazoyl, benzoxadiazoyl, naphthoxadiazoyl, benzofuranyl, benzisoxazoyl, tetrahydrobenzopyranyl, naphthyridinyl, indoyl or quinazolinyl, indanyl, tetrahydronaphthyl, tetrahydroisoquinolinyl, imidazothioazolyl all of which may be substituted or unsubstituted by one, two or three of any

of the following: halogen, CF_3, NO_2, CN, C_{1-3} alkyl, C_{1-3} alkoxy, NR_5R_6, $CONR_7R_8$, $CO_2(C_{1-3}$ alkyl), $COCF_3$, COR_{11}.

R_2 is preferably hydrogen, Cl, Br, CF_3, or C_{1-2} alkyl.

R_3 and R_4 are preferably hydrogen or C_{1-3} alkyl.

R_5 and R_6 are preferably hydrogen or C_{1-3} alkyl.

R_9 is preferably hydrogen or C_{1-3} alkyl.

R_{11} is preferably hydrogen or C_{1-3} alkyl.

X is preferably O.

n is preferably 1.

Preferred compounds are:

N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-2,3-dihydro-1H-indene-4-sulfonamides;

N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-2,3-dihydro-1H-indene-5-sulfonamides;

N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-5,6,7,8-tetrahydro-1-naphthalenesulfonamide;

N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-5,6,7,8-tetrahydro-2-naphthalenesulfonamide;

N-[3-{[(3R)-1-Methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-2-(trifluoroacetyl)-1,2,3,4-tetrahydro-7-isoquinolinesulfonamide;

N-[3-{[(3R)-1-Methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-2,1,3-benzothiadiazole-4-sulfonamide;

5-Chloro-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-1-naphthalenesulfonamide;

6-Chloro-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]imidazo[2,1-b][1,3]thiazole-5-sulfonamide;

5-Chloro-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-2,1,3-benzoxadiazole-4-sulfonamide;

5-Chloro-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-1,2-benzisoxazole-4-sulfonamide;

5-(Dimethylamino)-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-1-naphthalenesulfonamide;

N-[3-{[(3R)-1-Methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]naphtho[2,1-d][1,2,3]oxadiazole-5-sulfonamide;

N-[3-{[(3R)-1-Methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-2,1,3-benzoxadiazole-4-sulfonamide;

N-[3-{[(3R)-1-Methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-2-naphthalenesulfonamide;

N-[3-{[(3R)-1-Methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-1-naphthalenesulfonamide;

N-[3-{[(3R)-1-Methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-8-quinolinesulfonamide;

6-Chloro-N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)imidazo[2,1-b][1,3]thiazole-5-sulfonamide;

N-[3-{[(3R)-1-Methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-1-benzothiophene-3-sulfonamide;

N-[3-{[(3R)-1-Methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]dibenzo[b,d]furan-2-sulfonamide;

N-(4-Chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)dibenzo[b,d]furan-2-sulfonamide;

2,2,5,7,8-Pentamethyl-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-3,4-dihydro-2H-chromene-6-sulfonamide;

N-[3-{[(3R)-1-Methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-2-oxo-2H-chromene-6-sulfonamide;

5-Chloro-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-2-naphthalenesulfonamide;

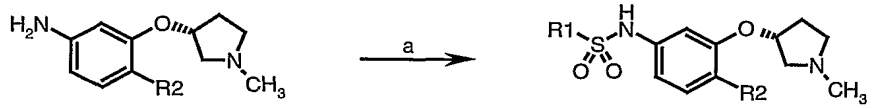
3-Bromo-5-formyl-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-4,5,6,7-tetrahydrothieno[3,2-c]pyridine-2-sulfonamide;

3-Bromo-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-4,5,6,7-tetrahydrothieno[3,2-c]pyridine-2-sulfonamide;

6-Chloro-2-(1,1-dimethylethyl)-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-1,3-benzoxazole-7-sulfonamide.

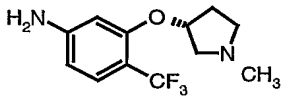
Compounds of Formula (I) may be prepared as outlined in Scheme 1.

Scheme 1

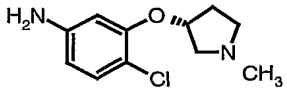


a) $R1SO_2Cl$, py, MeCN

Anilines **A** and **B** have been previously described: WO 2002089792 A1, incorporated by reference herein.



Aniline **A**



Anline **B**

Sulfonyl chlorides, when not commercially available, can prepared by methods known in the art: Shahripour, A.B. et al. *Bioorg. Med. Chem.* **2002**, *10*, 31; Cross, P.E. et al. *J. Med. Chem.* **1978**, *21*, 845; Huntress et al *J. Amer. Chem. Soc.* **1941**, *63*, 3446; Hashimoto, H. et al *J. Med. Chem.* **2002**, *45*, 1511; O'Brien, P. M. et al. *J. Med. Chem.* **2000**, *43*, 156; Brundish, D. *J. Med. Chem.* **1999**, *22*, 4584.

With appropriate manipulation, including the use of alternative nitrogen protecting group(s), the synthesis of the remaining compounds of Formula (I) was accomplished by methods analogous to those above and to those described in the Experimental section.

In order to use a compound of the Formula (I) or a pharmaceutically acceptable salt thereof for the treatment of humans and other mammals it is normally formulated in accordance with standard pharmaceutical practice as a pharmaceutical composition.

Compounds of Formula (I) and their pharmaceutically acceptable salts may be administered in a standard manner for the treatment of the indicated diseases, for example orally, parenterally, sub-lingually, transdermally, rectally, via inhalation or via buccal administration.

Compounds of Formula (I) and their pharmaceutically acceptable salts which are active when given orally can be formulated as syrups, tablets, capsules and lozenges. A syrup formulation will generally consist of a suspension or solution of the compound or salt in a liquid carrier for example, ethanol, peanut oil, olive oil, glycerine or water with a flavoring or coloring agent. Where the composition is in the form of a tablet, any pharmaceutical carrier routinely used for preparing solid formulations may be used. Examples of such carriers include magnesium stearate, terra alba, talc, gelatin, agar, pectin, acacia, stearic acid, starch, lactose and sucrose. Where the composition is in the form of a capsule, any routine encapsulation is suitable, for example using the aforementioned carriers in a hard gelatin capsule shell. Where the composition is in the form of a soft gelatin shell capsule any pharmaceutical carrier routinely used for preparing dispersions or suspensions may be

considered, for example aqueous gums, celluloses, silicates or oils and are incorporated in a soft gelatin capsule shell.

Typical parenteral compositions consist of a solution or suspension of the compound or salt in a sterile aqueous or non-aqueous carrier optionally containing a parenterally acceptable oil, for example polyethylene glycol, polyvinylpyrrolidone, lecithin, arachis oil, or sesame oil.

Typical compositions for inhalation are in the form of a solution, suspension or emulsion that may be administered as a dry powder or in the form of an aerosol using a conventional propellant such as dichlorodifluoromethane or trichlorofluoromethane.

A typical suppository formulation comprises a compound of Formula (1) or a pharmaceutically acceptable salt thereof which is active when administered in this way, with a binding and/or lubricating agent, for example polymeric glycols, gelatins, cocoa-butter or other low melting vegetable waxes or fats or their synthetic analogues.

Typical transdermal formulations comprise a conventional aqueous or non-aqueous vehicle, for example a cream, ointment, lotion or paste or are in the form of a medicated plaster, patch or membrane.

Preferably the composition is in unit dosage form, for example a tablet, capsule or metered aerosol dose, so that the patient may administer to themselves a single dose.

Each dosage unit for oral administration contains suitably from 0.1 mg to 500 mg/Kg, and preferably from 1 mg to 100 mg/Kg, and each dosage unit for parenteral administration contains suitably from 0.1 mg to 100 mg, of a compound of Formula (I) or a pharmaceutically acceptable salt thereof calculated as the free acid. Each dosage unit for intranasal administration contains suitably 1-400 mg and preferably 10 to 200 mg per person. A topical formulation contains suitably 0.01 to 1.0% of a compound of Formula (I).

The daily dosage regimen for oral administration is suitably about 0.01 mg/Kg to 40 mg/Kg, of a compound of Formula (I) or a pharmaceutically acceptable salt thereof calculated as the free acid. The daily dosage regimen for parenteral administration is suitably about 0.001 mg/Kg to 40 mg/Kg, of a compound of the Formula (I) or a pharmaceutically acceptable salt thereof calculated as the free acid. The daily dosage regimen for intranasal administration and oral inhalation is suitably about 10 to about 500 mg/person. The active ingredient may be administered from 1 to 6 times a day, sufficient to exhibit the desired activity.

These sulphonamide analogs may be used for the treatment of congestive heart failure, stroke, ischemic heart disease (angina, myocardial ischemia), cardiac arrhythmia, hypertension (essential and pulmonary), renal disease (acute and chronic renal failure/end stage renal disease) along with peripheral vascular disease (male erectile dysfunction, diabetic retinopathy,

intermittent claudication/ischemic limb disease) and ischemic/hemorrhagic stroke, COPD, restenosis, asthma, neurogenic inflammation, migraine, metabolic vasculopathies, bone/cartilage/joint diseases, arthritis and other inflammatory diseases, fibrosis (e.g. pulmonary fibrosis), sepsis, atherosclerosis, dyslipidemia, addiction, schizophrenia, cognitive disorders/Alzheimers disease, impulsivity, anxiety, stress, depression, pain, neuromuscular function, diabetes, gastric reflux, gastric motility disorders, ulcers and genitourinary diseases.

The urotensin antagonist may be administered alone or in conjunction with one or more other therapeutic agents, said agents being selected from the group consisting of endothelin receptor antagonists, angiotensin converting enzyme (ACE) inhibitors, A-II receptor antagonists, vasopeptidase inhibitors, diuretics, digoxin, and dual non-selective β-adrenoceptor and α_1-adrenoceptor antagonists.

No unacceptable toxicological effects are expected when compounds of the invention are administered in accordance with the present invention.

The biological activity of the compounds of Formula (I) are demonstrated by the following tests:

Radioligand binding:

HEK-293 cell membranes containing stable cloned human and rat GPR-14 (20 ug/assay) were incubated with 200 pM [125I] h-U-II (200 Ci/mmol^{-1} in the presence of increasing concentrations of test compounds in DMSO (0.1 nM to 10 uM), in a final incubation volume of 200 ul (20 mM Tris-HCl, 5 mM MgCl2). Incubation was done for 30 minutes at room temperature followed by filtration GF/B filters with Brandel cell harvester. ^{125}I labeled U-II binding was quantitated by gamma counting. Nonspecific binding was defined by ^{125}I U-II binding in the presence of 100 nM of unlabeled human U-II. Analysis of the data was performed by nonlinear least square fitting.

Ca^{2+}-mobilization:

A microtitre plate based Ca^{2+}-mobilization FLIPR assay (Molecular Devices, Sunnyvale, CA) was used for the functional identification of the ligand activating HEK-293 cells expressing (stable) recombinant GPR-14. The day following transfection, cells were plated in a poly-D-lysine coated 96 well black/clear plates. After 18-24 hours the media was aspirated and Fluo 3AM-loaded cells were exposed to various concentrations (10 nM to 30 uM) of test compounds followed by h-U-II. After initiation of the assay, fluorescence was read every second for one minute and then every 3 seconds for the following one minute. The inhibitory concentration at 50% (IC50)was calculated for various test compounds.

Inositol phosphates assays:

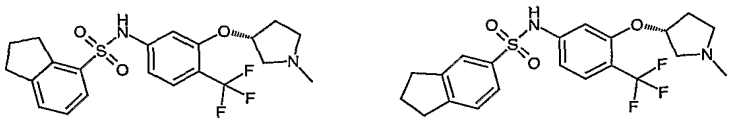
HEK-293-GPR14 cells in T150 flask were prelabeled overnight with 1 uCi myo-[^{3}H] inositol per ml of inositol free Dulbecco's modified Eagel's medium. After labeling, the cells were washed twice with Dulbecco's phosphate-buffered saline (DPBS) and then incubated in DPBS containing 10 mM LiCl for 10 min at 37°C. The experiment was initiated by the addition of increasing concentrations of h-U-II (1 pM to 1μM) in the absence and presence of three different concentrations (0.3, 1 and 10 uM) of test compounds and the incubation continued for an additional 5 min at 37°C after which the reaction was terminated by the addition of 10% (final concentration) trichloroacetic acid and centrifugation. The supernatants were neutralized with 100ul of 1M Trizma base and the inositol phosphates were separated on AG 1-X8 columns (0.8 ml packed, 100-200 mesh) in formate phase. Inositol monophosphate was eluted with 8 ml of 200 mM ammonium formate. Combined inositol di and tris phosphate was eluted with 4ml of 1M ammonium formate/ 0.1 M formic acid. Eluted fractions were counted in beta scintillation counter. Based on shift from the control curve K_B was calculated.

Activity for the compounds of this invention range from (radioligand binding assay): Ki = 1 nM – 10000 nM.

The following Examples are illustrative but not limiting embodiments of the present invention.

Example1

N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-2,3-dihydro-1H-indene-4- and -5-sulfonamides

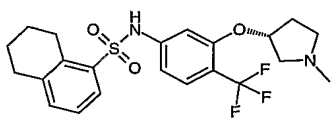


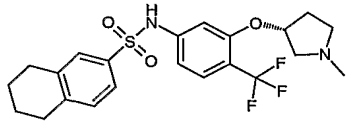
A solution of a mixture 2,3-dihydro-1H-indene-4- and -5-sulfonylchlorides [prepared by adding 2,3-dihydro-1H-indene to neat chlorosulfonic acid at –10 °C] (0.5 g, 2.3 mmol) in acetonitrile (2 mL) was added slowly (5 min) to a stirred solution of (R)-3-(1-methyl-3-pyrrolidinyl)-4-trifluoromethylaniline (0.6 g, 2.3 mmol) and pyridine (187 μL, 2.3 mmol). The mixture was stirred for 1.5 h at ambient temperature then concentrated under reduced pressure. Water (~10 mL) was added to the residue, and the mixture was made basic with saturated sodium bicarbonate, then extracted with ethyl acetate. The ethyl acetate extract was washed with water, brine, dried ($MgSO_4$) concentrated under reduced pressure to provide a solid residue. The crude solid was recrystallized from acetonitrile/water to yield a gray crystalline solid (0.94 g, 93%) consisting of a mixture of the two positional isomers. The two isomers were separated by Supercritical Fluid Chromatography (SFC) [Chiralpak AD, 21x25 mm, 10μ;

15% MeOH (0.5% isopropylamine); 50 mL/min, 30 °C; 100 bar op; uv 254 nm]. Isolated 130.3 mg of the 4-sulfonamido isomer: mp 138-141 °C. MS (ES) m/e 441 $[M+H]^+$ and 349.4 mg of the 5-sulfonamido isomer: mp 169-171 °C. MS (ES) m/e 441 $[M+H]^+$.

Example 2

N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-5,6,7,8-tetrahydro-1- and -2-naphthalenesulfonamides

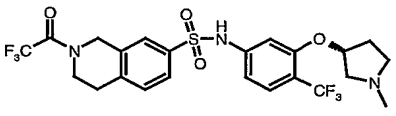
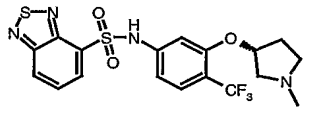
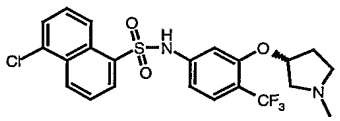


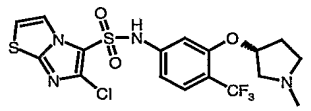
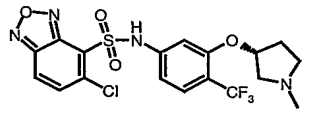
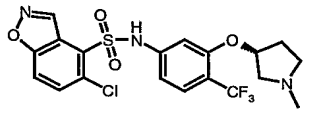
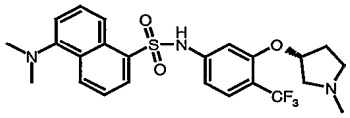
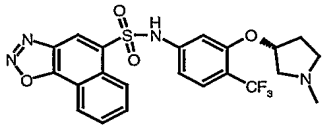
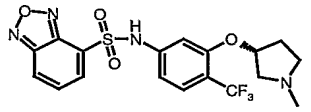
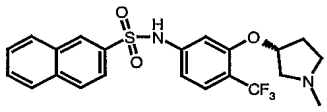
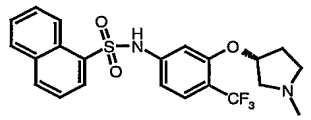


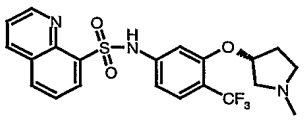
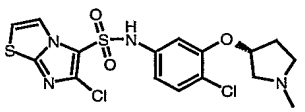
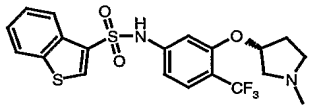
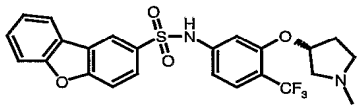
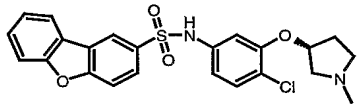
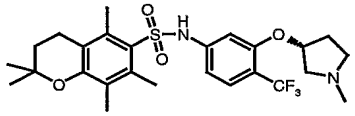
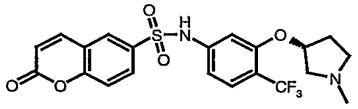
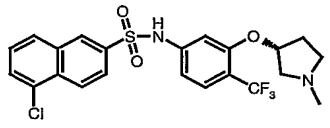
The tetrahydronaphthalenesulfonamide positional isomers were prepared exactly as described in Example 1 starting with 1,2,3,4-tetrahydronaphthalene, etc. The isomers were separated by SFC to provide: -1-naphthalenesulfonamido isomer (170.5 mg): mp 143-145 °C. MS (ES) m/e 454 $[M+H]^+$, and -2-naphthalene-sulfonamido isomer (302.2 mg): mp 163-165 °C. MS (ES) m/e 454 $[M+H]^+$.

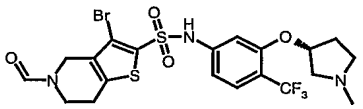
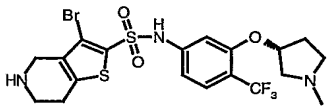
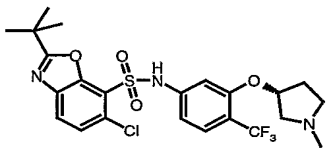
Examples 3-24

The following sulfonamides can be prepared according to Example 1 by reacting the appropriate sulfonyl chlorides with the anilnes in either acetonitrile or dichloro-methane.

#	structure	name	m/z
3		N-[3-{[(3R)-1-Methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-2-(trifluoroacetyl)-1,2,3,4-tetrahydro-7-isoquinolinesulfonamide	551
4		N-[3-{[(3R)-1-Methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-2,1,3-benzothiadiazole-4-sulfonamide	459
5		5-Chloro-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-1-naphthalenesulfonamide	485

6		6-Chloro-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]imidazo[2,1-b][1,3]thiazole-5-sulfonamide	481
7		5-Chloro-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-2,1,3-benzoxadiazole-4-sulfonamide	477
8		5-Chloro-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-1,2-benzisoxazole-4-sulfonamide	477
9		5-(Dimethylamino)-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-1-naphthalenesulfonamide	494
10		N-[3-{[(3R)-1-Methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]naphtho[2,1-d][1,2,3]oxadiazole-5-sulfonamide	493
11		N-[3-{[(3R)-1-Methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-2,1,3-benzoxadiazole-4-sulfonamide	443
12		N-[3-{[(3R)-1-Methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-2-naphthalenesulfonamide	451
13		N-[3-{[(3R)-1-Methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-1-naphthalenesulfonamide	451

14		N-[3-{[(3R)-1-Methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-8-quinolinesulfonamide	452
15		6-Chloro-N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)imidazo[2,1-b][1,3]thiazole-5-sulfonamide	447
16		N-[3-{[(3R)-1-Methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-1-benzothiophene-3-sulfonamide	457
17		N-[3-{[(3R)-1-Methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]dibenzo[b,d]furan-2-sulfonamide	491
18		N-(4-Chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)dibenzo[b,d]furan-2-sulfonamide	457
19		2,2,5,7,8-Pentamethyl-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-3,4-dihydro-2H-chromene-6-sulfonamide	527
20		N-[3-{[(3R)-1-Methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-2-oxo-2H-chromene-6-sulfonamide	469
21		5-Chloro-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-2-naphthalenesulfonamide	485

22		3-Bromo-5-formyl-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-4,5,6,7-tetrahydrothieno[3,2-c]pyridine-2-sulfonamide	568
23		3-Bromo-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-4,5,6,7-tetrahydrothieno[3,2-c]pyridine-2-sulfonamide	540
24		6-Chloro-2-(1,1-dimethylethyl)-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-1,3-benzoxazole-7-sulfonamide	531

Example 25

Formulations for pharmaceutical use incorporating compounds of the present invention can be prepared in various forms and with numerous excipients. Examples of such formulations are given below.

Tablets/Ingredients	Per Tablet
1.Active ingredient (Cpd of Form. I)	40 mg
2.Corn Starch	20 mg
3.Alginic acid	20 mg
4.Sodium Alginate	20 mg
5.Mg stearate	1.3 mg
	2.3 mg

Procedure for tablets:

Step 1: Blend ingredients No. 1, No. 2, No. 3 and No. 4 in a suitable mixer/blender.

Step 2: Add sufficient water portion-wise to the blend from Step 1 with careful mixing after each addition. Such additions of water and mixing until the mass is of a consistency to permit its conversion to wet granules.

Step 3: The wet mass is converted to granules by passing it through an oscillating granulator using a No. 8 mesh (2.38 mm) screen.

Step 4: The wet granules are then dried in an oven at 140°F (60°C) until dry.

Step 5: The dry granules are lubricated with ingredient No. 5.

Step 6: The lubricated granules are compressed on a suitable tablet press.

Inhalant Formulation

A compound of Formula I, (1 mg to 100 mg) is aerosolized from a metered dose inhaler to deliver the desired amount of drug per use.

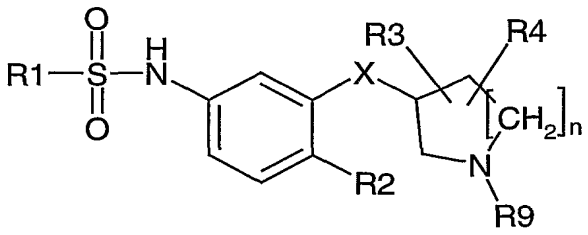
Parenteral Formulation

A pharmaceutical composition for parenteral administration is prepared by dissolving an appropriate amount of a compound of formula I in polyethylene glycol with heating. This solution is then diluted with water for injections Ph Eur. (to 100 ml). The solution is then sterilized by filtration through a 0.22 micron membrane filter and sealed in sterile containers.

The above specification and Examples fully disclose how to make and use the compounds of the present invention. However, the present invention is not limited to the particular embodiments described hereinabove, but includes all modifications thereof within the scope of the following claims. The various references to journals, patents and other publications which are cited herein comprise the state of the art and are incorporated herein by reference as though fully set forth.

What is claimed is:

1. A compound of Formula (I):



Formula (I)

wherein:

R_1 is naphthyl, quinolinyl, benzothiophenyl, benzthiadiazoyl, benzoxadiazoyl, naphthoxadiazoyl, benzofuranyl, dibenzofuranyl, benzothiazoyl, benzoxazoyl, benzisoxazoyl, tetrahydrobenzopyranyl, chromenonyl, tetrahydrothienopyridinyl, benzimidazoyl, benzodioxanyl, benzodioxoyl, benzodioxepinyl, naphthyridinyl, indoyl or quinazolinyl, indanyl, tetrahydronaphthyl, tetrahydroisoquinolinyl, imidazothioazolyl substituted or unsubstituted by one, two , three, four or five of any of the following: halogen, CF_3, OCF_3, SCF_3, NO_2, CN, C_{1-6} alkyl, C_{1-6} alkoxy, NR_5R_6, $CONR_7R_8$, SC_{1-6} alkyl, $CO_2(C_{1-6}$ alkyl), C_{1-6} alkyl-$CO_2(C_{1-6}$ alkyl), $COCF_3$, COR_{11};

R_2 is hydrogen, halogen, CF_3, CN, or C_{1-4} alkyl;

R_3, R_4, are independently hydrogen, C_{1-6} alkyl, benzyl, $-C(R_{13})_2-OR_{11}$, $-COOR_{12}$, $-CONR_{11}$, $-C(R_{13})_2-N(R_{11})_2$;

R_7, and R_8 are independently hydrogen, C_{1-6} alkyl, or benzyl;

R_5 and R_6, are independently hydrogen or C_{1-6} alkyl;

R_9 is hydrogen, C_{1-6} alkyl, or $-(CH_2)_mR_{14}$;

R_{11} is hydrogen or C $_{1-6}$ alkyl;

R_{12} is C $_{1-6}$ alkyl;

R_{13} is independently hydrogen or C_{1-3}alkyl;

R_{14} is phenyl, OH, or-$(C=O)C_{1-3}$alkyl;

X is O, S, or CH_2;

n is 0, 1 or 2;

m is 1 or 2;

provided that when R_{14} is OH, m is 2;

or a pharmaceutically acceptable salt thereof.

2. A compound of Claim 1 wherein:

R_1 is naphthyl, quinolinyl, benzothiophenyl, benzthiadiazoyl, benzoxadiazoyl, naphthoxadiazoyl, benzofuranyl, benzisoxazoyl, tetrahydrobenzopyranyl, naphthyridinyl, indoyl or quinazolinyl, indanyl, tetrahydronaphthyl, tetrahydroisoquinolinyl, imidazothioazolyl all of which may be substituted or unsubstituted by one, two or three of any of the following: halogen, CF_3, NO_2, CN, C_{1-3} alkyl, C_{1-3} alkoxy, NR_5R_6, $CONR_7R_8$, $CO_2(C_{1-3}$ alkyl), $COCF_3$, COR_{11};

R_2 is hydrogen, Cl, Br, CF_3, or C_{1-2} alkyl;

R_3 and R_4 are hydrogen or C_{1-3} alkyl;

R_5 and R_6 are hydrogen or C_{1-3} alkyl;

R_9 is hydrogen or C_{1-3} alkyl;

R_{11} is hydrogen or C_{1-3} alkyl;

X is O; and

n is 1.

3. A compound of Claim 1 chosen from:

N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-2,3-dihydro-1H-indene-4-sulfonamides;

N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-2,3-dihydro-1H-indene-5-sulfonamides;

N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-5,6,7,8-tetrahydro-1-naphthalenesulfonamide;

N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-5,6,7,8-tetrahydro-2-naphthalenesulfonamide;

N-[3-{[(3R)-1-Methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-2-(trifluoroacetyl)-1,2,3,4-tetrahydro-7-isoquinolinesulfonamide;

N-[3-{[(3R)-1-Methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-2,1,3-benzothiadiazole-4-sulfonamide;

5-Chloro-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-1-naphthalenesulfonamide;

6-Chloro-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]imidazo[2,1-b][1,3]thiazole-5-sulfonamide;

5-Chloro-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-2,1,3-benzoxadiazole-4-sulfonamide;

5-Chloro-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-1,2-benzisoxazole-4-sulfonamide;

5-(Dimethylamino)-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-1-naphthalenesulfonamide;

N-[3-{[(3R)-1-Methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]naphtho[2,1-d][1,2,3]oxadiazole-5-sulfonamide;

N-[3-{[(3R)-1-Methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-2,1,3-benzoxadiazole-4-sulfonamide;

N-[3-{[(3R)-1-Methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-2-naphthalenesulfonamide;

N-[3-{[(3R)-1-Methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-1-naphthalenesulfonamide;

N-[3-{[(3R)-1-Methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-8-quinolinesulfonamide;

6-Chloro-N-(4-chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)imidazo[2,1-b][1,3]thiazole-5-sulfonamide;

N-[3-{[(3R)-1-Methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-1-benzothiophene-3-sulfonamide;

N-[3-{[(3R)-1-Methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]dibenzo[b,d]furan-2-sulfonamide;

N-(4-Chloro-3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}phenyl)dibenzo[b,d]furan-2-sulfonamide;

2,2,5,7,8-Pentamethyl-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-3,4-dihydro-2H-chromene-6-sulfonamide;

N-[3-{[(3R)-1-Methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-2-oxo-2H-chromene-6-sulfonamide;

5-Chloro-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-2-naphthalenesulfonamide;

3-Bromo-5-formyl-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-4,5,6,7-tetrahydrothieno[3,2-c]pyridine-2-sulfonamide;

3-Bromo-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-4,5,6,7-tetrahydrothieno[3,2-c]pyridine-2-sulfonamide;

6-Chloro-2-(1,1-dimethylethyl)-N-[3-{[(3R)-1-methyl-3-pyrrolidinyl]oxy}-4-(trifluoromethyl)phenyl]-1,3-benzoxazole-7-sulfonamide.

4. A pharmaceutical composition comprising a compound of formula (I) of claim 1 and a pharmaceutically acceptable carrier or excipient.

5. A method of treating conditions associated with Urotensin-II imbalance by antagonizing the Urotensin-II receptor which comprises administering to a patient in need thereof, a compound of Formula I of claim 1.

6. A method according to Claim 5 wherein the disease is congestive heart failure, stroke, ischemic heart disease , angina, myocardial ischemia, cardiac arrhythmia, essential and pulmonary hypertension, renal disease, acute and chronic renal failure, end stage renal disease, peripheral vascular disease, male erectile dysfunction, diabetic retinopathy, intermittent claudication/ischemic limb disease, ischemic/hemorrhagic stroke, COPD, restenosis, asthma, neurogenic inflammation, migraine, metabolic vasculopathies, bone/cartilage/joint diseases, arthritis and other inflammatory diseases, fibrosis, pulmonary fibrosis, sepsis, atherosclerosis, dyslipidemia, addiction, schizophrenia, cognitive disorders, Alzheimers disease, impulsivity, anxiety, stress, depression, parkinsons, movement disorders, sleep-wake cycle, incentive motivation, pain, neuromuscular function, diabetes, gastric reflux, gastric motility disorders, ulcers and genitourinary diseases.

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Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

(88) Date of publication of the international search report:
21 October 2004

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: SULFONAMIDES

(57) Abstract: The present invention relates to sulfonamides, pharmaceutical compositions containing them, and their use as antagonists of urotensin II.

WO 2004/043369 A3

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US03/35364

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : C07D 401/12, 403/12, 211/24, 207/12; A61K 31/4015, 31/4025, 31/4439
US CL : 548/518, 541; 546/276.4, 278.4, 290; 514/343, 345, 424

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 548/518, 541; 546/276.4, 278.4, 290; 514/343, 345, 424

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
STN CAS Databases Online: FILE Registry, FILE Caplus (structure searches)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 6,423,717 B1 (BROMIDGE et al) 23 July 2002 (23.07.2002), columns 2-6.	2

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
16 March 2004 (16.03.2004)	02 SEP 2004
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (703)305-3230	Authorized officer Alan Rotman Telephone No. 703.308.1235

Form PCT/ISA/210 (second sheet) (July 1998)

Continuation of Box I Reason 2:
In these claims, the numerous variables (e.g. X, R1, R2, R3, R4, R5, R6, R7, R8, R9, n, m, etc), their voluminous complex meanings, their seemingly endless permutations and combinations make it virtually impossible to determine the full scope and complete meaning of the claimed subject matter. As presented, the claimed subject matter cannot be regarded as being a clear and concise description for which protection is sought and as such the listed claims do not comply with the requirements of PCT article 6. Thus it is impossible to carry out a meaningful search on same. A search will be made on the first discernable invention of claim 2.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US03/35364

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claim Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claim Nos.: 1 and 3-6
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
Please See Continuation Sheet

3. ☐ Claim Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.